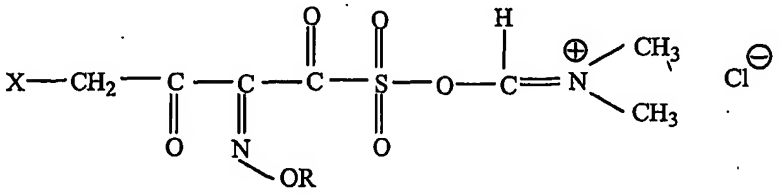
Claims :

1. A novel 4-halo-2-oxyimino-3-oxo butyric acid-N, N-dimethyl formiminium chloride chlorosulfate of formula (I) useful in the preparation of cephalosporin antibiotics



(I)

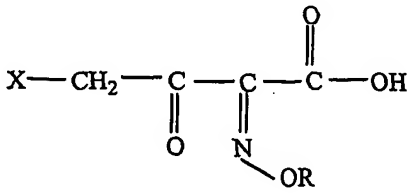
wherein

X is chlorine or bromine;

R is hydrogen, C_{1-4} alkyl group, an easily removable hydroxyl protective group, $-CH_2COOR_5$, or $-C(CH_3)_2COOR_5$

wherein R_5 is hydrogen or an easily hydrolysable ester group.

2. A process for preparation of compound of formula (I) comprising reacting 4-halo-2-oxyimino-3-oxobutyric acid of formula (IV^1),



(IV^1)

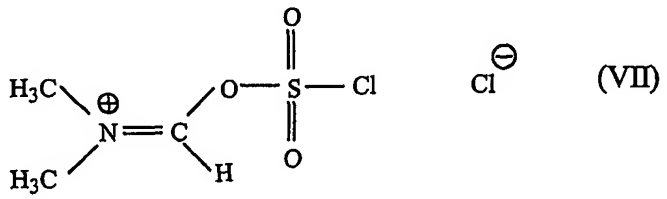
wherein

X is chlorine or bromine;

R is hydrogen, C_{1-4} alkyl group, an easily removable hydroxyl protective group, $-CH_2COOR_5$, or $-C(CH_3)_2COOR_5$

wherein R_5 is hydrogen or an easily hydrolysable ester group.

with N, N-dimethylformiminium chloride chlorosulphate of formula (VII)



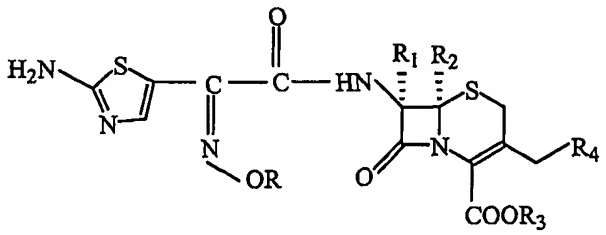
(VII)

in an organic solvent at a temperature ranging from -30^0 C to -15^0 C.

3. A process according to Claim 2, wherein the organic solvent is selected from chlorinated solvents such as dichloromethane, dichloroethane, or chloroform; aromatic hydrocarbons such as benzene or toluene; and nitriles such as acetonitrile, propionitrile or butyronitrile.

4. A process according to Claim 2, wherein the molar ratio of compound of formula (VII) to compound of formula (IV^1) is between 1.1 to 1.3.

5. A process for preparation of a cephalosporin compound of formula (II),



(II)

wherein

R is hydrogen, C_{1-4} alkyl group, an easily removable hydroxyl protective group, -CH_2COOR_5, or -C $(CH_3)_2COOR_5$

wherein R_5 is hydrogen or an easily hydrolysable ester group.

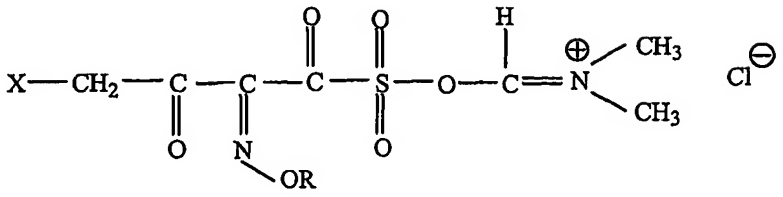
R_1 is hydrogen or $-OCH_3$;

R_2 is hydrogen;

R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester, or an alkali or alkaline earth metal,

R_4 is hydrogen or is a substituent useful in cephalosporin chemistry;

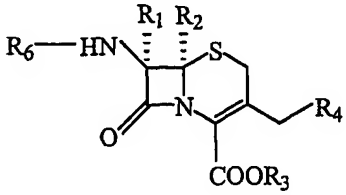
comprising reaction of compound of formula (I)



(I)

wherein X is chlorine or bromine; R is hydrogen, C $_{1-4}$ alkyl group, an easily removable hydroxyl protective group, $-CH_2COOR_5$, or $-C(CH_3)_2COOR_5$, wherein R_5 is hydrogen or an easily hydrolysable ester group

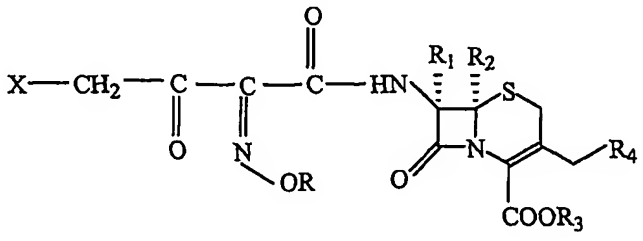
with 7-amino cephalosporanic acid of formula (V),



(V)

wherein R_1 is hydrogen or $-OCH_3$; R_2 is hydrogen; R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester, or an alkali or alkaline earth metal, or is a silyl group; R_4 is hydrogen or is a substituent useful in cephalosporin chemistry; R_6 is hydrogen or a silyl group with the proviso that, when R_3 is hydrogen R_6 is also hydrogen; when R_3 is a silyl group R_6 is also a silyl group; and when R_3 is an ester, or an alkali or alkaline earth metal R_6 is hydrogen

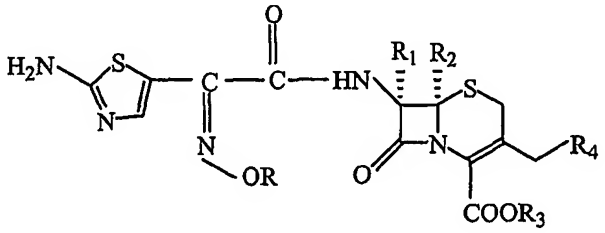
to give 7-[(4-halo-2-oxyimino-3-oxobutyramido-3-substituted-3-cephem-4-carboxylic acid of formula (VIII),



(VIII)

wherein X, R, R_1, R_2 and R_4 have the same meanings as defined hereinearlier, and R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester, or an alkali or alkaline earth metal.

followed by cyclisation of compound (VIII) with thiourea to give compound of formula (II),



(II)

wherein R and R_5 are as defined above; R_1 is hydrogen or $-OCH_3$; R_2 is hydrogen; R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester or an alkali or alkaline earth metal; R_4 is hydrogen or is a substituent useful in cephalosporin chemistry.

6. A process according to Claim 5, wherein the reaction of compound (I) and compound (V) to give compound (VIII) is carried out in an organic solvent and in the presence of a base at a temperature ranging from -80^0 C to -15^0 C,.

7. A process according to Claims 5 or 6, wherein the organic solvent is selected from chlorinated solvents such as dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbons such as benzene and toluene; nitrile solvents such as acetonitrile, propionitrile and butyronitrile; ethers such as tetrahydrofuran and dioxane.

8. A process according to Claims 5 or 6, wherein the base is selected from N, N dimethyl aniline, diethyl amine, and pyridine.

9. A process according to Claims 5 or 6, wherein the molar ratio of compound (I) to the cephalosporin compound (V) is between 1.1 to 2.0, preferably between 1.2 to 1.5.

10. A process according to Claims 5 or 6, wherein the preferred temperature is between –55^0 C to –25^0 C.

11. A process according to Claim 5, wherein the reaction of compound (VIII) and thiourea to give the cephalosporin compounds of formula (II) is carried out in a mixture of organic solvent and water and in the presence of a base at low to ambient temperature.

12. A process according to Claims 5 or 11, wherein the the organic solvent is selected from chlorinated solvents such as dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbons such as benzene and toluene; nitrile solvents such as acetonitrile, propionitrile and butyronitrile; ethers such as tetrahydrofuran and dioxane.

13. A process to Claims 5 or 11, wherein the base is selected from alkali metal carbonates, such as sodium carbonate, potassium carbonate and lithium carbonate; alkali metal hydrogen carbonates, such as sodium hydrogen carbonate and potassium carbonate; and alkali metal acetates, such as sodium acetate and potassium acetate.

14. A process according to Claims 5 or 11, wherein the temperature is between –5^0 C to 40^0 C, preferably between –10^0 C to 30^0 C.

15. A process according to Claim 5, wherein the compound of formula (II) is any one of

i) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid i.e. cefdinir,

ii) 7-[(Z)-2-(2-amino-4-thiazolyl)-2-methoxyimino)acetyl]amino-3-[(1Z)-2-(4-methyl-5-thiazolyl)ethenyl -3-cephem-4-carboxylic acid, i.e. cefditoren and the pivaloyloxymethyl ester i. e. cefditoren pivoxil,

iii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-methylpyrrrolodino) methyl-3-cephem-4-carboxylate i.e. cefepime,

iv) 7-[(Z)-2-(2-aminothiazol-4-yl)methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylic acid i.e. cefetamet, and the pivaloyloxymethyl ester i. e. cefetamet pivoxil,

v) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid i.e. cefixime,

vi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[1-methyl–1H-tetrazol-5-yl]thio]methyl]-3-cephem-4-carboxylic acid i.e. cefmenoxime,

vii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[[5-carboxymethyl)-4-methyl-2-thiazolyl]thio]methyl]- 3-cephem-4-carboxylic acid i.e. cefodizime,

viii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,3-dihydro-2-(2-hydroxyethyl)-3-imino-1H-pyrazol-1-yl]methyl]- 3-cephem-4-carboxylic acid i. e. cefoselis,

ix) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporanic acid i.e. cefotaxime,

x) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[92,3-cyclopenteno-1-pyridinium)methyl]- 3-cephem-4-carboxylic acid i.e. cefpirome,

xi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate- i.e. cefpodoxime and the 1-methylethoxycarbonyloxy ether i. e. cefpodoxime proxetil,

xii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl-5,6,7-tetrahydroquinolinium-4-carboxylic acid inner salt i. e. cefquinome,

xiii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methylethyl)oximinoacetamido}-3-[pyridinium]methyl-3-cephem-4-carboxylacid acid inner salt i. e. ceftazidime,

xiv) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(5-methyl-1,2,3,4-tetrazoyl)-methyl-3- cephem-4-carboxylic acid i. e. cefteram and the and the pivaloyloxymethyl ester i. e. cefteram pivoxil,

xv) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[(2-furanylcarbonyl)thio]methyl]- 3- cephem-4-carboxylic acid i. e. ceftiofur,

xvi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylic acid i. e. ceftizoxime,

xvii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid i. e. ceftriaxone, and

xviii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1,2,3-thiadiazol-5-ylthio)methyl]- 3-cephem-4-carboxylic acid i. e. cefuzonam.